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# Discontinuation of antimicrobial therapy in adult neutropenic haematology patients: A prospective cohort

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ABSTRACT

*Objectives:* Antibiotics for febrile neutropenia (FN) in acute myeloid leukaemia (AML) patients undergoing intensive chemotherapy are usually maintained until neutropenia resolution, because of the risk of uncontrolled sepsis in this vulnerable population. This leads to unnecessarily prolonged antimicrobial therapy.

*Methods:* Based on ECIL-4 recommendations, we modified our management strategy and discontinued antibiotics after a pre-established duration in patients treated for a first episode of FN between August 2014 and October 2017.

*Results:* Antibiotics were stopped during 62 FN episodes, and maintained in the control group (n = 13). Median age of patients was 54 years. A total of 39 (63%) patients received induction and 23 (37%) consolidation chemotherapy; 36 (58%) patients had fever of unknown origin. Median neutropenia length was 26 days (IQR 24–30). Antibiotics were started at day 9 (IQR 5–13). Most patients received piperacillin-tazobactam (56%) or cefepime (32%). Antimicrobial therapy was longer in the control group than in the policy compliant group, 10 (IQR 7–16) vs. 19 days (IQR 15–23), $P = 0.0001$. After antibiotics discontinuation, 20% patients experienced fever recurrence, within 5.5 days (IQR 3–7.5). None of these febrile episodes were severe and 80% patients remained afebrile, with neutrophil recovery occurring within 5 days (IQR 2–8.5). Overall, 287 antibiotics days were spared; this represents 49% of all days with antibiotics. No patient had died at day 30 from intervention; six died during late follow-up, two from graft-versus-host disease and four from relapsed or refractory leukaemia.

*Conclusions:* Discontinuing antibiotics in neutropenic AML patients treated for a first episode of FN is safe, and results in significant antibiotic sparing.

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## 1. Introduction

Acute myeloid leukaemia (AML) patients undergoing intensive chemotherapy are considered at high risk for severe infections because of a deep ($<0.1 \times 10^9$/L) and prolonged (>7 days) neutropenia. Febrile neutropenia (FN) occurs in 70-80% of these patients [1,2]. As a result of neutropenia and the low bacterial inoculum, 60% of patients present with fever of unexplained origin (FUO), defined as fever with no clinical or microbiological documentation despite thorough investigations [1,2].

Initial treatment of FN should take into account previous documented infections, colonization with resistant bacteria, and hospital ecology. In our centre, according to US and European recommendations, we commonly use an escalation strategy, where initial empirical therapy is based on a beta-lactam covering typical Enterobacteriaceae and *Pseudomonas aeruginosa*, but not extended-spectrum beta-lactamase (ESBL), carbapenemase producers, or

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multiresistant non-fermenters. Therapy is escalated to carbapenems or with adjunction of aminoglycosides if the patient deteriorates, or if a resistant pathogen is isolated. Glycopeptides are used in seriously-ill patients (haemodynamic instability, severe pneumonia), in cases of colonization with methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, or penicillin-resistant *S. pneumoniae*, and in skin or soft-tissue or catheter-related infection [1,3].

The Infectious Diseases Society of America (IDSA) recommends maintaining antimicrobial therapy (AMT) until resolution of neutropenia (i.e. absolute neutrophil count [ANC] $> 0.5 \times 10^9$/L) [1]. This is justified by the risk of uncontrolled sepsis in this vulnerable population. However, it leads to prolonged AMT, which increases the risk of multiresistant bacteria selection, puts pressure on the colonising microbial flora, leading to colitis with *Clostridium difficile* or colonization with yeasts, and can be responsible for pharmacological toxicity, including encephalopathy or nephropathy [4-8]. Furthermore, non-bacterial agents, such as viruses or fungi, may cause some of these undocumented febrile episodes. Some episodes may also have a non-infectious origin, such as acute transfusion reactions, or allergic reaction to chemotherapy.

Early studies addressing the issue of antibiotic discontinuation in neutropenic patients showed an increased risk of severe infection and mortality [9,10]. Therefore, antibiotic discontinuation was considered unsafe. However, these conclusions have been challenged by more recent studies. Fever recurrence has been shown to occur whether antibiotics are stopped during neutropenia or after its resolution, and that with appropriate AMT and monitoring, non-severe FUO has low mortality, even in high-risk haematology patients [11-14]. Therefore, the 4th European Conference on Infections in Leukaemia (ECIL-4) published guidelines stating that AMT can be discontinued after $\geq$72 h of intravenous (IV) treatment, in selected patients with non-severe FUO who are afebrile for $\geq$48 h, irrespective of the ANC or expected duration of neutropenia. If fever recurs, AMT should be started again promptly [3].

Based on these recommendations, we modified our management strategy for newly diagnosed adult AML patients receiving intensive chemotherapy: we treated these patients for a first episode of non-severe FN, and introduced AMT discontinuation after a pre-established duration, whatever the absolute ANC.

## 2. Material and methods

### 2.1. Population

Our antibiotic policy is reviewed and updated each year in discussions between haematologists, infectious diseases physicians and microbiologists. This antibiotic discontinuation policy was decided and implemented in August 2014. Although this paper reports results of a routine policy change and not a clinical study, for clarity we will use the terms “inclusion/included” to define patients concerned by the new policy and “exclusion/excluded” for those unconcerned by the policy.

We included consecutive patients who were admitted to our university hospital between August 2014 and October 2017. Inclusion criteria were age at least 18 years, new diagnosis of AML or myeloid sarcoma, first-line treatment with intensive chemotherapy, and first non-severe episode of FN, including FUO, primary bacteraemia and focal infections. The policy change also included patients who had an orthopaedic implant, had been admitted in the intensive care unit (ICU) for sepsis or septic shock during a previous hospital stay or were colonized with multiresistant bacteria. One patient could be included several times in our study, but during a different neutropenic episode and a different hospital stay (e.g. during induction and consolidation phases).

Exclusion criteria were acute lymphoblastic leukaemia (ALL) diagnosis, relapsed or refractory patients, previous hematopoietic stem-cell transplant (HSCT), non-intensive treatment, severe infection (i.e. sepsis or septic shock, according to the recent definition [15]), severe infection such as endocarditis or osteomyelitis, and presence of a prosthetic heart valve, as these patients were considered too frail and/or at higher risk for severe infectious complications. Antibiotics were maintained until resolution of neutropenia in these patients.

### 2.2. Antimicrobial therapy discontinuation

Initial empirical therapy was given intravenously (IV) in all cases. It was mostly based on a beta-lactam covering typical Enterobacteriaceae and *P. aeruginosa* (e.g. cefepime or piperacillin-tazobactam). Narrower-spectrum beta-lactam (cefotaxime) was used when fever occurred within the first week of hospitalization. Carbapenem or adjunction of an aminoglycoside was used if a resistant pathogen was isolated. Glycopeptides were used in cases of skin, soft-tissue or catheter-related infection.

AMT was discontinued after at least seven days of IV treatment, after resolution of clinical symptoms and at least five days of apyrexia, regardless of the ANC or the predicted duration of neutropenia. Duration of AMT was determined according to clinical presentation and/or microbiological documentation: seven days for FUO, colitis or pneumonia, 10 days for catheter-related infection or bacteraemia, 10 days for urinary tract infection in female patients, and 14 days for urinary tract infection in male patients. Patients were thoroughly monitored. In cases of febrile recurrence, administration of the same antibiotics was restarted immediately by ward nurses (a standing order enabled immediate treatment without medical prescription), and maintained until neutrophil recovery. Adjunction of antifungal treatment was discussed according to clinical presentation, duration of neutropenia, indirect fungal biomarkers (galactomannan antigen), and thoracic computed tomography (CT)-scan.

Antibiotic prophylaxis with fluoroquinolones was not administered because of the high level of resistance to fluoroquinolones in our population. All patients received antifungal prophylaxis with oral posaconazole during the neutropenic period.

### 2.3. Endpoint

The primary endpoint was the occurrence of a new febrile episode after AMT discontinuation. Secondary endpoints were number of days without antibiotics, occurrence of severe infections, and 30-days mortality.

### 2.4. Statistics

Data collected prospectively were analysed retrospectively. Outcomes were compared between the groups with the t test or Mann-Whitney U test for continuous outcomes and with the $\chi^2$ or Fisher’s exact test, as appropriate, for contingency analysis. *P*-values of 0.05 were considered significant. Statistical analysis was performed using Microsoft Excel v.12.2.8 (MS Office 2008) and GraphPad Prism v.7.0.

### 2.5. Ethics

This study was conducted in accordance with the ethical standards of our hospital committee on human experimentation, and with the Helsinki Declaration of 1975, as revised in 2008. We did not submit this study to a formally constituted review board because the subject of this article was the analysis of a major antibiotic policy change performed to follow European guidelines (ECIL-4) for AML patients. Per French law at the time, review of usual

**Table 1**
Patient characteristics.

| Population | Policy compliant group N = 36 | Control group N = 13 |
|---|---|---|
| Age, years | 52 [33–60] | 56 [49–66] |
| Females | 17 (47) | 3 (23) |
| Extended-Spectrum Beta-Lactamase colonization | 4 (11) | 0 (0) |
| Diagnosis | | |
| Acute Myeloloid Leukaemia | 34 (94) | 13 (100) |
| Other | 2 (6) | 0 (0) |
| Cytogenetics | | |
| High risk | 10 (28) | 8 (62) |
| Intermediate | 9 (25) | 3 (23) |
| Favourable | 17 (47) | 2 (15) |
| High tumour burden | 9 (25) | 4 (36) |

Data are N (%) or median [IQR]

care in monocentric studies did not require submission to an ethical review committee. The patients' usual physicians collected all data analysed as part of routine diagnosis and treatment.

## 3. Results

### 3.1. Flow-chart

A total of 98 patients eligible for intensive treatment were newly diagnosed with AML or myeloid sarcoma in our university hospital between August 2014 and October 2017. Each patient received at least one intensive treatment course (induction and/or consolidation). The number of hospital stays (hence, the number of neutropenic episodes) was 195 overall, as patients could be included more than once but over different hospital stays. Thirty-five neutropenic episodes were excluded because of hospitalization in the ICU due to AML complication or severe infection (sepsis or septic shock). During 45 neutropenic episodes, patients remained afebrile. Thus, a total of 115 episodes of non-severe FN were included. AMT was not discontinued in 66 episodes (58%): neutrophil recovery occurred before the planned end of antibiotic treatment in 35 episodes (30%); apyrexia was not achieved before neutrophil recovery in 18 episodes (16%); and in 13 episodes (11%), AMT was not stopped because of physicians' failure to follow the new policy. We chose to use these 13 episodes as a control group. AMT was effectively stopped in 49 non-severe FN episodes (Fig. 1).

### 3.2. Population

Patient characteristics are described in Table 1. Overall, 36 patients were included in the policy compliant group and 13 in the control group. Median age was 54 years (interquartile range [IQR] 36-63). Four patients (8%) had previous known ESBL colonization. Overall, 47 patients had AML, including eight with acute promyelocytic leukaemia (APL), one patient had biphenotypic AML treated as an AML, and one had myeloid sarcoma. Induction chemotherapy was based on anthracyclines, either daunorubicin, or idarubicin given during three to five days, in combination with cytarabine (200 mg/m$^2$/day) given by continuous IV infusion for seven days. One patient received amsacrine combined with cytarabine. Consolidation chemotherapy consisted of cytarabine alone, 1 to 3 g/m$^2$/12h over 3 days, according to physician judgment. APL patients were treated according to APL2006 protocol, or with arsenic trioxide in combination with all-trans retinoic acid.

### 3.3. Control group

Antibiotics were not stopped in 13 FN episodes (occurring in 13 patients) because of physicians' failure to follow the new policy. These patients were used as a control group. Reasons for maintaining antibiotics were because patients were considered too frail (n = 5), or uncontrolled infection (n = 1); no reasons were identified for the seven remaining patients. Although there were no statistically significant differences between the two groups, control patients had more aggressive underlying disease, with poor prognosis cytogenetics and higher tumour burden at admission (defined by either leukocyte count >50 G/l, intravascular disseminated coagulation, or spontaneous tumour lysis syndrome). This could explain physicians' reluctance to discontinue antibiotics in these patients.

**Table 2**
Febrile neutropenia, clinical and microbiological documentation.

| Febrile neutropenia episodes N = 62 | Policy compliant group N = 49 | Control group N = 13 |
|---|---|---|
| Treatment phase | | |
| Induction | 28 (57) | 11 (85) |
| Consolidation | 21 (43) | 2 (15) |
| FUO | 28 (56) | 8 (62) |
| Clinical symptoms | 12 (24) | 4 (31) |
| Upper respiratory tract infection | 3 (6) | 1 (8) |
| Catheter-related infection | 3 (6) | 1 (8) |
| Pneumonia | 3 (6) | 2 (18) |
| Colitis | 1 (2) | 0 |
| Dental abscess | 1 (2) | 0 |
| Endometritis | 1 (2) | 0 |
| Microbiological documentation | 13 (26) | 3 (23) |
| Bacteraemia | 7 (14) | 1 (8) |
| *Escherichia coli* | 4 (8) | 0 |
| *Enterobacter cloacae* | 1 (2) | 0 |
| *Streptococcus salivarius* | 1 (2) | 0 |
| *Streptococcus oralis* | 1 (2) | 0 |
| *Coagulase-negative staphylococci*[*] | 1 (2) | 1 (8) |
| Urinary tract infection | 2 (4) | 1 (8) |
| Female | | |
| *Enterococcus faecalis* | 1 (2) | 0 |
| *Escherichia coli* | 1 (2) | 0 |
| Male | | |
| *Klebsiella pneumoniae* | 0 | 1 (8) |
| Positive nasal swab | 3 (6) | 1 (8) |
| Positive catheter culture | 1 (2) | 0 |

[*] Several blood cultures were positive. Data are N (%). FUO: fever of unexplained origin

### 3.4. Febrile neutropenia

Febrile neutropenia occurred during induction therapy for 39 (63%) episodes and during consolidation therapy for 23 (37%) episodes. FUO occurred in 36 episodes (58%). Clinical symptoms were upper respiratory tract symptoms (n = 4), pneumonia (n = 5), catheter-related infection (n = 4), colitis (n = 1), dental abscess (n = 1) and endometritis (n = 1). We obtained microbiological documentation in 16 (26%) cases. Blood cultures were positive in eight patients, with Gram-negative rods (n = 5) or streptococci (n = 2), and one patient had concomitant *Escherichia coli* and *S. oralis* bacteraemia. Two patients had several positive blood cultures with coagulase-negative staphylococci (*Staphylococcus hominis* and *Staphylococcus epidermidis*). One patient had clinical signs of catheter infection, with significant *S. epidermidis* growth at removal and culture. Three asymptomatic patients had positive urine culture. One female patient presented with *E. coli* endometritis. In four patients with upper respiratory tract symptoms, nasal swab was positive for viruses (Table 2).

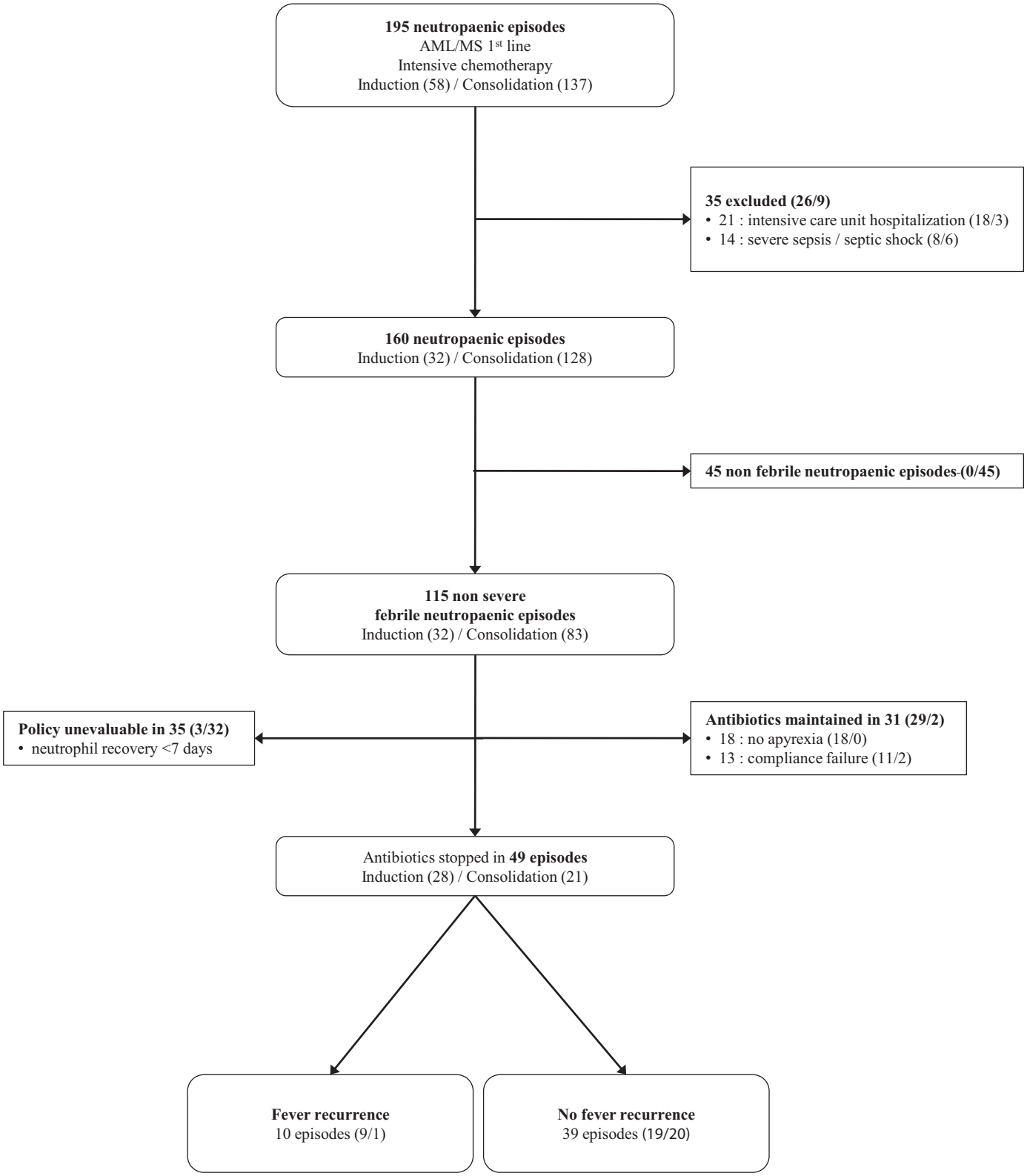


**Fig. 1.** Flow chart.
AML: acute myeloid leukaemia. MS: myeloid sarcoma
Numbers correspond to number of neutropenic episodes (induction phase/consolidation phase).

**Table 3**
Antimicrobial therapy.
Patients were mostly given beta-lactam-based antimicrobial therapy, administered as monotherapy or in combination with aminoglycosides and/or anti-methicillin-resistant staphylococci therapy, according to clinical presentation, known ESBL colonization or microbiological documentation. Some patients received two or more antibiotics; therefore, the sum of each value can exceed the overall number of patients in each group.

| | Policy compliant group N = 49 | Control group N = 13 |
|---|---|---|
| Antibiotics used | | |
| Cefotaxime | 3 (6) | 1 (8) |
| Monotherapy | 3 (6) | 1 (8) |
| Piperacillin-tazobactam | 27 (55) | 8 (62) |
| Monotherapy | 18 (37) | 8 (62) |
| + Amikacin | 6 (12) | 0 |
| + Vancomycin | 2 (4) | 0 |
| + Linezolid | 2 (4) | 0 |
| Cefepime | 16 (33) | 4 (31) |
| Monotherapy | 11 (22) | 4 (31) |
| + Amikacin | 3 (6) | 0 |
| + Vancomycin | 1 (2) | 0 |
| + Linezolid | 1 (2) | 0 |
| + Metronidazole | 1 (2) | 0 |
| Meropenem | 1 (2) | 0 |
| + Amikacin | 1 (2) | 0 |
| Others | 2 (4) | 0 |
| Vancomycin monotherapy | 1 (2) | 0 |
| Ceftriaxone – Metronidazole – Doxycycline | 1 (2) | 0 |
| Antimicrobial therapy length, by site | | |
| Fever of Unknown Origin | 7.5 [7–10] | 18 [14.5–20.5] |
| Pneumonia / upper respiratory tract infection | 13.5 [9–21] | 22.5 [19–28] |
| Catheter-related infection/bacteraemia | 10 [10–17.5] | 20.5 [19–22] |
| Male urinary tract infection | 10 [10–10] | – |
| Female urinary tract infection | 18 [18–18] | 24 [24–24] |
| Colitis | 14 [14–14] | – |
| Adverse events | 16 (33) | 4 (31) |
| Toxidermia | 5 (10) | 1 (8) |
| Abnormal liver function tests | 5 (10) | 1 (8) |
| *C. difficile* colitis | 2 (4) | 0 |
| Diarrhoea | 2 (4) | 1 (8) |
| Veinitis | 1 (2) | 0 |
| Acute renal failure | 1 (2) | 0 |
| Encephalopathy | 0 | 1 (8) |

Data are N (%) or median [IQR].

### 3.5. Antimicrobial therapy

Empirical AMT was initiated immediately after the first episode of FN. Four patients (6%) received cefotaxime as monotherapy (100 mg/kg/day IV divided in 3 doses). Most patients received antipseudomonal beta-lactam, either piperacillin-tazobactam, 4 g/6-8 h IV (n = 35, 56%) or cefepime, 2 g/8 h IV (n = 20, 32%), mostly given as monotherapy (n = 41, 66%). Combination therapy with amikacin was given in patients with known ESBL colonization (n = 5, 8%), or signs that indicate severe infection but without sepsis criteria, such as mottled skin (n = 3, 5%). Anti-methicillin-resistant staphylococci therapy (vancomycin or linezolid) was given in case of skin- or catheter-related infection (n = 6, 10%). One patient with ESBL colonization was given a carbapenem, meropenem. One patient with colitis was treated with cefepime and metronidazole. One patient received vancomycin alone for *S. hominis* bacteraemia. The patient diagnosed with *E. coli* endometritis initially received ceftriaxone, metronidazole, and doxycycline (Table 3). AMT was considered adequate, following standard guidelines for FN and according to our centre ecology, and when microbiological documentation was available, appropriate, in 46 (94%) patients in the policy compliant group and 12 (92%) in the control group.

As expected, effective AMT was longer in the control group. In the policy compliant group, antibiotics were discontinued as planned in FUO (n = 28; 7.5 days [IQR 7-10]) and catheter-related infections and/or bacteraemia (n = 10; 10 days [IQR 10-17]). However, for other clinical situations, antibiotics were given for longer than recommended. Reasons were persistence of clinical symptoms (n = 7) and fever recurrence (n = 2).

We observed adverse events in 20 (32%) patients; all were considered mild or moderate (Grade 1–2). Most of them were not specific, and may have been caused by anti-leukaemia chemotherapy.

### 3.6. Outcome

Median duration of neutropenia was 26 days (IQR 24–30) in the overall population, 27 days (IQR 25–34) for patients in the induction phase and 24 days (IQR 22–27) for patients in the consolidation phase (Table 4). One patient did not have neutrophil recovery and was discharged at day 43.

In the overall population, AMT was started a median of 9 days (IQR 5–13) following chemotherapy, and was given for 10 days (IQR 7–18). During the induction phase, AMT was started on day 6 (IQR 3–8), and given for 17 days (IQR 10–21); during consolidation, it was started on day 14 (IQR 11.5–17), and given for 9 days (IQR 7–10). AMT was administered for significantly longer in the control group compared with the policy compliant group: 19 days (IQR 15–23) vs. 10 days (IQR 7–16), $P = 0.0001$ (Fig. 2). This was true for both the induction and consolidation phases. There were no differences in neutropenia length, or antibiotic initiation day between the groups.

After AMT discontinuation, 10 patients (20%) in the policy compliant group experienced a new febrile episode and 39 (80%) achieved neutrophil recovery without febrile recurrence. Febrile

**Table 4**
Evolution

| | Policy compliant group N = 49 | Control group N = 13 |
|---|---|---|
| Neutropenia length, days | 26 [24–31] | 26 [21–27.5] |
| Induction | 27.5 [25–34.25] | 26 [22–28.5] |
| Consolidation | 24 [22–27] | 23 [21.5–24.5] |
| Antibiotic therapy initiation, Day | D9 [5.75–14.25] | D5.5 [3–9.25] |
| Induction | D6 [3–8.5] | D5 [3–6] |
| Consolidation | D14 [12–18] | D12 [11–13] |
| Antibiotic therapy length, days | 10 [7–16] | 19 [15–23] |
| Induction | 15 [8–19.25] | 26 [22–28.5] |
| Consolidation | 9 [7–10] | 23 [21.5–24.5] |
| Febrile recurrence after antibiotic discontinuation | 10 (20) | – |
| Induction | 9 (18) | – |
| Consolidation | 1 (2) | – |
| Delay between ATB stop and fever recurrence, days | 5.5 [3–7.5] | – |
| Induction | 6 [3–8] | – |
| Consolidation | 3 [3–3] | – |
| No febrile recurrence after antibiotic discontinuation | 39 (80) | – |
| Induction | 19 (39) | – |
| Consolidation | 20 (41) | – |
| Delay between ATB stop and neutrophil recovery, days | 5 [2–8.5] | – |
| Induction | 8 [4.5–12.5] | – |
| Consolidation | 2 [1–6] | – |

Data are N (%) or median [IQR]. ATB: antibiotic therapy.

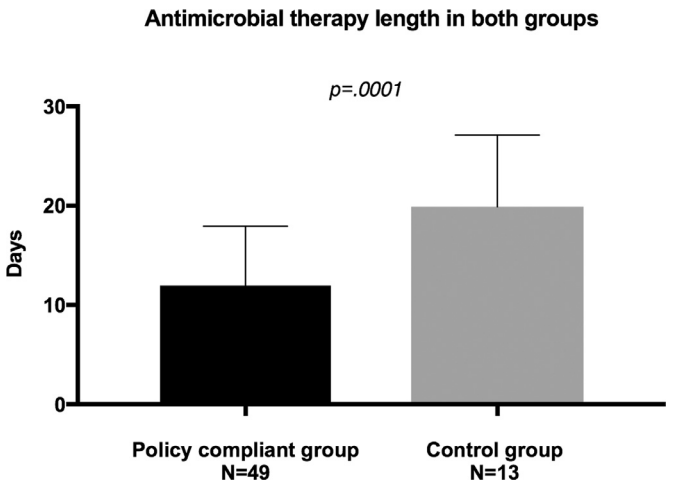


**Fig. 2.** Antimicrobial therapy length in the two groups.

recurrence occurred in 9 patients (18%) during the induction phase, and in 1 patient (2%) during consolidation. Treatment phase was not associated with significantly higher risk of fever recurrence ($P = 0.08$). Median duration between AMT interruption and new febrile episode was 5.5 days (IQR 3–7.5) in the overall population, 6 days (IQR 3–8) for the induction phase, and 3 days (IQR 3–3) for the consolidation phase. None of the 10 febrile episodes led to haemodynamic instability, septic shock, or ICU hospitalization. Eight episodes (80%) presented as FUO; febrile recurrence was asymptomatic but microbiologically documented in the two (20%) remaining patients: one had *E. coli* bacteraemia, and the other had *Streptococcus mitis* bacteraemia. Interestingly, both of these patients initially presented with FUO.

Use of relatively narrow-spectrum antibiotics, such as cefotaxime, was associated with higher risk of fever recurrence ($P = 0.0009$). However, use of monotherapy vs. combination therapy ($P = 0.43$) or use of penicillin vs. cephalosporin ($P = 0.9$) had no significant impact on risk of fever recurrence.

Patients who achieved neutrophil recovery without fever recurrence were equally distributed between the induction (n = 19, 39%) and consolidation (n = 20, 41%) phases. Median overall duration between AMT discontinuation and neutrophil recovery was 5 days (IQR 2–8.5), with 8 days (IQR 4.5–12.5) in the induction group and 2 days (IQR 1–6) in the consolidation group. As AMT is usually maintained until neutrophil recovery, this corresponds to the number of days of antibiotics spared. Patients received antibiotics for 845 days overall, and for 586 days in the policy-compliant population. Our management strategy enabled us to spare 287 days of AMT; this represents 34% of the overall consumption, and 49% for the policy-compliant population.

### 3.7. Mortality

No patient had died at day 30 from antibiotics discontinuation. Three-year overall survival (OS) was 75%. Median OS was not reached. Median follow-up was 19 months. Overall, six patients (12%) died during follow-up. Two patients underwent allogeneic stem-cell transplant and died of severe graft-versus-host disease at six and eight months after diagnosis, respectively. Four patients died of AML: three relapsed, and died 3 years, 19 months and 16 months after initial diagnosis, respectively; one had refractory leukaemia and died 10 months after diagnosis.

## 4. Discussion

The main result of our study is that discontinuing AMT in patients treated for a first episode of FN is safe, regardless of the ANC. Indeed, 80% patients remained afebrile until neutrophil recovery. Among the 20% of patients with a recurrent febrile episode, the outcome was favourable, without any severe sepsis, ICU admission or death. AMT was significantly longer in patients who were not compliant with the new policy. Implementation of the new strategy resulted in high antibiotic sparing, a mean of 6 days per patient, and this was similar in patients with or without a second febrile episode. In the policy compliant population, 49% of all days with antibiotics were spared.

Most of the first and second febrile episodes occurred remotely from each other. Febrile recurrences were diagnosed a median 6 days and up to 14 days after AMT discontinuation. These episodes are probably independent events; it is unlikely that the same microorganism caused both episodes. Blood cultures at the time of febrile recurrence were positive in only two patients, who both initially presented as FUO. Previous studies reported that recurrence of fever might occur whether or not AMT is discontinued [9,11,12]. Patients probably present several infectious episodes, caused by different microorganisms, during prolonged neutropenia and this may be another reason to discontinue AMT as it might enable better microbiological documentation and lead to de-escalation therapy.

ECIL-4 guidelines state that AMT can be discontinued after at least three days of IV treatment in patients with non-severe FUO who are afebrile for at least 48 h. Before these guidelines, standard of care in our unit was to discontinue AMT after neutrophil recovery. Changing clinical practices is challenging, particularly in the absence of randomized controlled study to support these paradigm-changing recommendations. We decided to adapt the guidelines to our centre habits, hoping for a better appropriation by our prescribers. We thus chose to discontinue AMT after at least seven days of IV treatment and five days of apyrexia. In contrast, we extended indications of antibiotic discontinuation to cases of documented fever, whereas ECIL-4 recommendations only refer to FUO episodes, which concerned 58% of our population.

However, in our study, 35 (30%) patients were excluded because of neutrophil recovery before AMT cessation, with most of these

patients (91%) in the consolidation phase. This high number of excluded patients could reflect the longer duration of antibiotic therapy used in this study compared with ECIL-4 guidelines, and indicates that we could probably align our strategy more closely to ECIL-4 guidelines. This is particularly true for patients in the consolidation phase, who are probably a lower risk group with shorter neutropenic period. A tighter application of ECIL-4 guidelines could probably save even more AMT days.

Discontinuation of AMT in neutropenic patients is not a new topic, but remains controversial. Pizzo et al., in 1979, provided the first study addressing this issue [9]. They included 33 patients with FUO after chemotherapy for solid neoplasia or haemopathy, randomized between stopping or continuing treatment after seven days of empirical AMT. Seven patients (41%) in the experimental arm relapsed, with five documented febrile episodes, and two septic deaths due to *E. coli* bacteraemia, vs. only one fever recurrence and no deaths in the standard group. Antibiotic discontinuation was thus considered unsafe in neutropenic patients. Later, Cherif et al., in 2004, conducted a randomized study among 60 high- and low-risk haematology patients, in which empirical AMT was stopped after 48 h of apyrexia [11]. They showed that febrile recurrence occurred in both neutropenic (9/49, 18%) and non-neutropenic (2/11, 18%) patients. One neutropenic patient died from an invasive fungal infection. A study by Slobbe et al. included 169 high-risk haematology patients receiving fluoroquinolone and fluconazole prophylaxis [12]. Imipenem was stopped after ≤72 h in cases of FUO, or switched to narrower spectrum antimicrobial agents according to microbial documentation. There were no differences between fever recurrence, severe infections or death among the different groups. ECIL-4 guidelines based on these studies and others were published in 2013 [9-14,16-19].

To our knowledge, few prospective studies on this subject have been published since 2013. One prospective French study by Micol et al. included seven high-risk neutropenic patients with FUO. Antimicrobial therapy was discontinued after a mean of 15 days, which is longer than the ECIL-4 recommendations; four patients remained afebrile, with neutrophil recovery achieved within two to four days, and three patients had recurrent fever in less than three days, with one septic shock. AMT was spared for a mean of three days, but the authors considered that exposing patients to a risk of uncontrolled secondary infections was unethical. However, interpretation of this study is controversial, and was commented by others [20,21]. It is noteworthy that the patient undergoing septic shock was the only one receiving salvage therapy, underlying the importance of patient selection.

Recently, a Spanish team conducted a multicentric, randomized study in 157 high-risk neutropenic haematology patients with FUO [22]. AMT was stopped after ≥72 h of apyrexia in the experimental group, or withdrawn at neutrophil recovery. Mean AMT length was 11.9 days in the experimental group and 14.4 days in the control group. This enabled a significant sparing of 2.5 days of AMT ($P = 0.026$). The frequency of recurrent fever was similar in both groups, (11 patients [14%] in the experimental group and 14 [18%] in the control group, $P = 0.54$), with only one severe infection; no patient died after AMT withdrawal. However, in our opinion, this study has some limits. First, the overall population was heterogeneous, and included patients who were at lower risk for FN (81 patients, 52%), such as patients receiving chemotherapy for lymphoid malignancies, including autologous stem cell transplant; these patients are expected to have duration of neutropenia of 7 days or more, but neutropenia is usually not as deep as in AML patients or allogeneic stem cell recipients (76 patients, 48%). There were more low-risk patients in the control group; therefore, neutropenia was of shorter duration, 11 (8.0–21.3) days vs. 14 (9.5–24) days in the experimental group. Second, only 41 (53%) patients were still neutropenic at AMT withdrawal in the experimental group; the reason for this is unclear. Although results of this study are encouraging, this may limit extrapolation of these findings. Interestingly, our median antibiotic duration (10 days) was similar to that reported in this study, despite having a longer apyrexia requirement before AMT discontinuation.

A French observational study included 82 cases of FN; antibiotics were discontinued whatever the ANC, according to ECIL-4 guidelines. Forty-eight (58%) FUO episodes did not relapse during hospital-stay and 14 (17%) had fever recurrence, without excessive in-hospital mortality or ICU admission [23]. Rates of fever recurrence were similar to that observed in our study, and in others published before ECIL-4 guidelines [9-14,16-19]. Another study, conducted by la Martire et al., aimed to evaluate the impact of an antibiotic stewardship intervention on antibiotic consumption. Antibiotic discontinuation was performed among 52/100 FN episodes. Surprisingly, no fever recurrence during the same neutropenic episode was observed. Compared with our population, neutropenia was of significantly shorter duration (19 [12–29] vs. 26 [24–31] days); this could explain the higher fever recurrence rates observed in our study [24].

Management of FN has changed over the past years. The prudent use of AMT is justified by the global increase in antibiotic resistance in hospitalized patients and in the community. Several studies have shown that antibiotic stewardship leads to improved AMT use, and decreases antibiotic consumption [25,26]. Antibiotic resistance is a special concern for haematology patients, who undergo several chemotherapy-induced neutropenia episodes, and are exposed to repeated courses of broad-spectrum AMT [27-29].

Our study has limitations. First, it is a monocentric cohort based on a small population. Nevertheless, our patients are standard AML patients, included consecutively, who reflect the overall population of patients with AML. Second, the lack of a control group with patients recruited prospectively limits the impact of our results. However, having observed no adverse effect at all of the new strategy, a control group could not have yielded better results. One of the reasons may be the automatic standing order for readministration of AMT in patients with a new febrile episode. Third, this study, following a policy change, might be biased in patient selection. However, in our centre, only two haematology physicians manage AML patients, with twice weekly rounds by a consulting infectious disease physician, resulting in homogenous management of the patients.

## 5. Conclusions

In conclusion, antibiotic discontinuation in patients newly diagnosed with AML presenting a first episode of FN after receiving intensive chemotherapy is feasible and safe, provided that appropriate AMT is started again promptly after fever recurrence. This strategy reduces antibiotic use, and does not increase the rate of severe infections or mortality in high-risk haematology patients.

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## Competing Interests

None

## Ethical Approval

Not required

## Authorship

CBe, HD and SA formulated the research question, and designed the study.

CBo, SBo, MN, BC, CL, SBa, PC, AS, AW, JBB, LR, KJW, GE, NB and IA included patients, collected data for tolerance, efficacy and follow-up.

ZV included patients, collected and analysed data, and wrote the manuscript draft.

CBe, SA, BQ and MT revised the manuscript.

All authors read and approved the final version of this manuscript.

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